UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 25 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Toxicity Review of One Non-guideline Study
EPA Reg. No.: 72674-E
2-Butyl-1,2-benzisothiazolin-3-one
DP Barcode: D274986
Case: 062095

From: Chris Jiang, Chemist, CJ
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To: Marshall Swindell, PM 33
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Thru: Winston Dang, Team Leader
Team One, RASSB/AD [7510C] 6/18/2001

and

Norman J. Cook
Norm Cook, Chief, RASSB/AD [7510C] 06/25/01

Applicant: Avecia Inc., Wilmington, DE

FORMULATION:

Active Ingredient:	% by weight
2-Butyl-1,2-benzisothiazolin-3-one	97.8 %
Inert Ingredient(s)	2.2 %
Total	100.0 %

Laboratory: Zeneca Central Toxicology Laboratory, Cheshire, United Kingdom

Applicant: Avecia Inc., Wilmington, DE

ACTION REQUESTED:

Review the following toxicity study [MRID 443649-19] for the oral versus dermal assessment of the test compound, 2-butyl-1,2-benzisothiazolin-3-one.

CONCLUSION:

The dermal exposure equivalent would probably be similar to the value obtained through the oral route assuming the test material is 100 % absorbed through the skin.

The summary is listed below. A complete data evaluation review is attached.

Summary:

1. Assessment of Oral versus Dermal Toxicity of 2-Butyl-1,2-benzisothiazolin-3-one (MRID 443649-19)

SUMMARY: In MRID 443649-19, the oral dose route for Dolphin Fungicide (97.8 % a.i.) has been substituted for the dermal route of exposure because of the severe dermal irritation produced.

In an acute oral toxicity study of S123386, 3 out of 5 male and 1 out of 5 female rats died after doses of 5000 mg/kg of S123386, and 1 out of 5 female rats died after doses of 2000 mg/kg; therefore, the oral LD_{50} was estimated to be 4267 mg/kg for males and 4732 mg/kg for females[1].

In an acute dermal toxicity study, irritation was observed but there were no signs of systemic toxicity so the dermal LD_{50} was concluded to be in excess of the limit dose of 2000 mg/kg[2].

When dermally exposed to S123386 for 4 hours, lesions that marked by sub-epithelial fibrosis and chronic irritation, indicating that the test substance is dermally corrosive[3].

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[1]Lees, D. (1996). Substance S123386: Acute Oral Toxicity in Rats. Zeneca Central Toxicology Laboratory. Report No. CTL/P/5067.

[2]Lees, D. (1996). Substance S123386: Acute Dermal Toxicity in the Rat. Zeneca Central Toxicology Laboratory. Report No. CTL/P/4992.

[3]Lees, D. (1996). Substance S123386: Skin Irritation in the Rabbit. Zeneca Central Toxicology Laboratory. Report No. CTL/P/4969.

These studies indicate that S123386 although of low acute oral and dermal toxicity is corrosive to the skin which, therefore, limits the doses that can be used in a systemic subchronic toxicity study. Consequently, the oral route was chosen for the toxicological assessment.

In a 90-day feeding study, rats received diets containing 40, 200, or 2000 ppm (equivalent to 3.1 and 3.4; 15.3 and 16.6; and 149.2 and 162.4 mg/kg/day for males and females, respectively). At doses of 2000 ppm, there was a marked reduction in body weight associated with reduced food uptake. At that dose level, signs of toxicity included stomach mucosal irritation, increased liver weight, and increased alkaline phosphatase (ALP) activity. No adverse effects were seen at the other dose levels; therefore, it was concluded that the highest dose with no adverse effects (NOAEL) was 200 ppm (15.3 mg/kg/day for males and 16.6 mg/kg/day for females[4]).

On the basis of the comparison between the acute oral and dermal toxicity data, it would be reasonable to conclude that under the conditions of repeated daily dosing for 90 days, the dermal exposure to S123386 that would be required to produce signs of systemic toxicity would be similar to the oral lowest effect level, that is, 149.2 mg/kg/day assuming the test material was 100 % absorbed through the skin. Therefore, the dermal equivalent of a NOAEL would be similarly achieved through an oral route, about 15 mg/kg/day.

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[4]Rattray, NJ. (1997). S123386: 90-day Feeding Study in the Rat. Zeneca Central Toxicology Laboratory. Report No. CTL/P/5280.